Decision Summary

CMS has determined that there is sufficient evidence to conclude that the use of osmotic blood brain barrier disruption (BBBD) used as part of a treatment regimen for brain tumors in Medicare beneficiaries is not reasonable and necessary under Section 1862(a)(1)(A) of the Social Security Act.

Accordingly, we are issuing a national coverage determination (NCD) that states:

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Decision Memo

TO: Administrative File: CAG #00333N
Blood Brain Barrier Disruption (BBBD)

FROM:

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group

Louis Jacques, MD
Division Director

LCDR Tara Turner, PharmD
Lead Analyst

James Rollins, MD, MSHA, PhD
Lead Medical Officer

SUBJECT: Final Coverage Decision Memorandum for Osmotic Blood Brain Barrier Disruption (BBBD) when used as part of a treatment regimen for brain tumors

DATE: March 20, 2007

I. Decision

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II. Background

We are providing a descriptive summary of brain tumors, chemotherapy for brain tumors, the blood brain barrier (BBB), and methods for its disruption so that readers who are unfamiliar with this concept can better understand this memorandum.

Blood brain barrier disruption

The blood-brain barrier (BBB) is a physiologic barrier that protects the brain from toxic substances, including most chemotherapeutic agents. It is created by the tight junctions between endothelial cells that line the capillaries in the brain. Factors important in determining drug-entry into the brain include molecular weight as well as lipid solubility. The BBB normally prevents passage of drugs with molecular weights greater than 180 Daltons. The BBB may be partly responsible for the poor efficacy of chemotherapy for malignant primary or metastatic brain tumors.

BBBD is the disruption of the tight junctions between the endothelial cells that line the capillaries in the brain, accomplished by osmotic disruption, bradykinin or irradiation (Neuwelt; Frenkel, Diehl, et al.1980; Van Vulpen, Kal, Taphoorn, El-Sharoun, 2002; Kemper, Boogerd, Thuis et al. 2004). Osmotic disruption of the BBB, the most common technique, has revealed that separation of the cerebral endothelial tight junctions can occur, which will allow transmission of higher molecular weight molecules, as well as substances which are less lipophilic, into the brain. This decision is only evaluating osmotic disruption. Any use of BBBD throughout this document and decision relates only to osmotic BBBD.

Mannitol is the most commonly used BBBD agent; this infusion is usually delivered into either the internal carotid or vertebral artery, depending on the tumor's arterial supply, via percutaneous femoral artery catheterization. The rate and duration of mannitol infusion are critical for successful barrier disruption. After barrier disruption occurs, contrast dye is infused to document the location and extent of barrier altercation. Chemotherapeutic agents are given in conjunction with barrier disruption. Repeated treatments are given monthly as needed. Serial scans of the brain are performed to monitor the progress of treatment. While the mannitol administration is central, the BBBD process includes all items and services necessary to perform the procedure, including hospitalization, monitoring, and repeated imaging procedures.

Title XVIII of the Social Security Act defines coverage of drugs used in an anticancer chemotherapeutic regimen in section 1861(t)(2). Mannitol is not an anticancer chemotherapeutic drug.

As noted below, the use of radiation for the treatment of brain tumors is associated with cognitive deficits. One claimed benefit of BBBD to enhance the delivery of chemotherapy is the avoidance of radiation. This could result in preservation of cognitive function, or perhaps even improvement in cognitive deficits. Proponents claim that BBBD followed by chemotherapy can improve the effectiveness of care, quality of life and survival for patients with brain tumors.

Most of the published research on the use of BBBD as part of a treatment regimen for brain tumors has been based on studies involving Primary Central Nervous System Lymphoma (PCNSL). PCNSL is a high-grade B cell malignancy that presents within the neuroaxis without evidence of systemic lymphoma. The prognosis of PCNSL is poor compared to histologically similar lymphoma occurring outside the central nervous system (CNS). As noted in a study by Roman-Goldstein and associates, the incidence of central nervous system lymphoma has been increasing in both immunologically competent and immunologically compromised patients (e.g., transplant recipients or patients with AIDS) (Roman-Goldstein, Jones, Delashaw, McMenomey et al. 1998). As this disease shows increasing incidence, atypical clinical and radiological presentations will occur. Though not commonly found in the cavernous sinus region or internal auditory canal, PCNSL is included in the differential diagnosis of these regions. This tumor is relatively rare; standardized guidelines for the baseline evaluation and response assessment of PCNSL are lacking, thus complicating comparability among clinical trials. Abrey and colleagues, as well as other international groups, have formulated recommendations to outline consensus opinion regarding baseline evaluation for all patients, standardize response criteria and outcomes measures for patient enrolled in clinical trails, and to review clinical issues unique to PCNSL (Abrey, Batchelor, Ferreri, Gospodarowicz, et al. 2005).

Incidence and epidemiology of brain tumors

Brain tumors are the third leading cause of cancer deaths in men ages 20 to 39 and fifth leading cause in women of that age. Some authors have noted that brain tumors might be better termed "intracranial neoplasms" since some do not arise from brain tissue (DeAngelis, 2001). We recognize the reasonableness of this point and discuss the various origins of these neoplasms later in this section. Similarly, because the brain is part of the CNS these tumors are sometimes also referred to as CNS tumors or CNS neoplasms. We preferably use the term brain tumors in this decision memorandum as we believe that using this simpler terminology will facilitate the general public's understanding of this document. However, we use the other terms when greater precision is needed.

The American Cancer Society estimates that 18,820 malignant tumors of the brain or spinal cord (10,730 in men and 8,090 in women) will be diagnosed during 2006 in the United States (ACS 2006). Approximately 12,820 people (7,260 men and 5,560 women) will die from these malignant tumors (a mortality rate of 6 per 100,000). This type of cancer accounts for approximately 1.3% of all cancers and 2.2% of all cancer-related deaths. Both adults and children are included in these statistics.

According to the National Cancer Institute (NCI), the incidence and mortality rates for cancers that originate in the brain and CNS has remained relatively unchanged in the last decade (SEER 2006). Both incidence and mortality rates are substantially higher for Whites than for other racial/ethnic groups. Regardless of racial/ethnic group, men have higher incidence and mortality rates than women. Brain and other CNS cancers are the second leading cause of cancer-related death in children and make up 21 percent of all childhood cancers. In comparison to adults, the absolute number of brain and CNS cancer deaths in children is smaller and survival rates are higher.

According to the NCI, between 1973 and 1985, the total age-adjusted cancer incidence in the United States (all races, men and women) rose by 10.7%, with an average annual percentage change of +0.9% (Greig, Ries, Yancik, Rapoport, 1990). Analysis of the reported age-specific incidence of primary malignant brain tumors over that same period of time revealed that incidence rates increased dramatically between 1973/1974 and 1985. Compared to 1973/1974, the 1985 incidence of primary malignant brain tumors increased for persons aged 75-79, 80-84, and 85 years of age by 187%, 394%, and 501%, respectively. Similar increases were found in both men and women, analyzed separately and in combination. Average annual percentage changes in primary brain tumor incidence were +7.0%, +20.4%, and +23.4% in these age ranges, respectively. The incidence of primary brain cancer in younger persons varied little over the same period of time. Two possible causes have been hypothesized that might explain the increased incidence in the elderly: the introduction and extensive use of x-ray computed tomography since 1973 that may account for the detection of more tumors and/or a true increase in incidence occurring independently of diagnostic advances.

Both environmental factors (e.g., ionizing radiation, immunosuppression, exposure to vinyl chloride, benzene and other organic compounds, heavy metals,), as well as genetic risk factors (e.g., neurofibromatosis, tuberous sclerosis, Multiple Endocrine Neoplasia type 1) have been implicated in development of brain tumors (Salvatore Weitberg, Mehta, et al. 1996; Moss, 1985; Tomlinson, 1997; Young, Povey 1998; Gutmann, Aylsworth, Carey et al. 1997). Transplant recipients and patients with the acquired immunodeficiency syndrome (AIDS) have substantially increased risks for PCNSL (Levin, Leibel, Gutin, 2001; Schabet M, 1999).

Classification of brain tumors

Tumors involving the brain can be categorized as primary (tumors originating in the brain), or secondary (tumors arising from other organs and metastasizing to the brain). The World Health Organization (WHO) classifies CNS tumors by their patterns of differentiation and presumed cell of origin (see Appendix C). Approximately 70% of symptomatic primary CNS tumors arise within the substance (parenchyma) of the brain and spinal cord. The remainders arise within the tissues surrounding the brain (meninges), pituitary or pineal glands. Glial cell tumors are the most common brain tumors. Examples of neuroepithelial tumors that are likely to occur in the elderly include astrocytomas, glioblastomas, ependymal tumors, and oligodendrogliomas. Recent evidence has suggested that oligodendrogliomas may be more common than previously thought; this is of importance because these tumors are chemosensitive. Glial tumors account for 50 to 60% of primary tumors, meningiomas account for 25%, schwannomas for 10%, and all other CNS tumors for the remainder.

Occasionally, CNS tumors arise from cells not considered central nervous system in nature. About 1 in 4 patients with cancer will develop tumors that spread to the CNS, though some note that brain metastases outnumber primary neoplasms by at least 10 to 1, and may occur in 20% to 40% of cancer patients (Patchell 2003). These tumors include germ cell tumors (histologically identical to those of testicular or ovarian origin), PCNSL: both of which originate in the brain as well as metastatic tumors (originate from outside the brain). The most common primary cancers metastasizing to the brain include lung cancer (50%), breast cancer (15 to 20%), cancers of unknown primary sites (10 to 15%), melanoma (10%), and colon cancer (5%) (Patchell 2003; (Nelson JS, Von Deimling A, Peteren 2000), though almost any cancer has that potential. Metastatic tumors typically arise where the white and gray matter of the brain meet. The symptoms depend upon the function of the affected part of the brain; they can include headaches, seizures, or no symptoms at all, when first detected. About 15% of patients who die of cancer have symptomatic brain metastasis; an additional 5% suffer spinal cord involvement.

The histologic type, the location of the cancer, and the general condition of the patient determine what therapy is appropriate for patients with brain tumors. The three main therapeutic strategies include surgery, radiotherapy, and chemotherapy. Other therapeutic categories under development include immunotherapy, gene therapy, and antiangiogenesis therapy.

Although surgery for patients with brain or spinal cord tumors is rarely curative, it is the most important treatment for patients with accessible tumors other than PCNSL. Surgery can be used to confirm a diagnosis, relieve intra-cranial pressure, and to improve symptoms as well as control seizures. Corticosteroid administration in association with surgery can also reduce the risk of worsening function by preventing postoperative swelling. The evidence seems to indicate that more complete surgical removal of a tumor improves both quality of life as well as survival. The exception to this rule is gliomas. According to Albert and associates, if a tumor exhibits contrast enhancement before surgery, a postoperative contrast-enhanced MRI scan obtained within 3 days of resection accurately predicts the extent of residual tumor and thereby helps to establish the prognosis. Surgeons' clinical estimates of the extent of resection are not thought to be reliable (Albert, Forsting, 1994).

The second mode of treatment for patients with brain tumors is radiotherapy. This form of treatment can be provided in a number of ways, and is often used when the entire primary tumor cannot be surgically removed. External-beam radiation (whole brain radiation therapy), the traditional form of radiation therapy, delivers radiation from outside of the body. Hyperfractionation is a modified form of external-beam radiation that involves applying less intense but more frequent doses of radiation. Some benign tumors are treated with external-beam radiation to prevent recurrence, even if the entire primary tumor has been surgically removed. They also may be treated with radiation at the time of recurrence.

Stereotactic (or stereotaxic) radiosurgery uses a large dose of radiation to destroy tumor tissue in the brain. High doses of radiation are directed precisely to the required areas. Most nearby tissues are not damaged by this procedure. Stereotactic radiosurgery can be done in one of three ways: a linear accelerator (high-energy photon radiation); gamma knife (cobalt 60); or heavy charged particle beams (e.g., protons and helium ions.) Stereotactic radiosurgery is most commonly used to treat small benign tumors as well as both primary and secondary brain cancers, and can be used either alone or along with whole-brain radiation therapy. Stereotactic radiotherapy uses the same approach as stereotactic radiosurgery to deliver radiation to the target tissue. However, stereotactic radiotherapy uses multiple small fractions of radiation as opposed to one large dose. Giving multiple smaller doses may improve outcomes and minimize side effects. The advantage of using targeted radiation is that the surrounding, healthy tissue is left undestroyed. It often is used in addition to external-beam radiation, especially in cases of malignant gliomas and metastases that are in deep or sensitive areas of the brain.

Though postoperative radiotherapy improves the quality of life and prolongs the duration of survival with high-grade tumors (e.g., anaplastic astrocytoma or glioblastoma multiforme), its role in patients with low-grade (particularly asymptomatic) tumors is uncertain. In asymptomatic patients with low-grade astrocytomas or oligodendrogliomas, radiotherapy is often postponed until symptoms develop. Some feel that conventional radiotherapy offers modest palliation (Alexander, Moriarty, Davis, Wen, 1995). There are recommendations that brain and spinal cord gliomas should be treated with high doses of irradiation (5,500 to 6,000 cGy for brain tumors, and 4,500 to 5,000 cGy for spinal tumors). Irradiation is applied to the tumor as well as the surrounding region. Stereotactic radiosurgery can be used to treat metastasis and to "boost" conventional irradiation for gliomas, though its efficacy has been difficult to establish (Chang Adler, Hancock, 1998).

One potential complication to patients being treated with radiotherapy for brain tumors is its potential effect on cognitive functions. This adverse event has been documented in children (Radcliffe J, Bunin GR, Sutton LN, 1994; Maddrey AM, Bergeron JA, Lombardo ER, et al., 2005) as well as in adults (Kramer, Crowe, Larson, et al. 1997; Laack, Brown, 2004). Meyers and Scheibel were one of the first to publish on this subject (Meyers, Scheibel, 1990). They noted that cancer patients often developed cognitive and behavioral alterations during or after radiation therapy, chemotherapy, or immunotherapy. They also note that some impairments are acute and reversible, while others persist after cessation of treatment or have a delayed onset. Gregor and associates also noted that neuropsychometric deficits are common after radiation treatment for brain tumors, and could be related to the timing of treatment, as well as the specific radiation technique (Gregor, Cull, Traynor, et al. 1996). And more recently, after noting that individuals with low-grade gliomas, PCNSL, and those undergoing prophylactic cranial irradiation for systemic malignancies often suffered neurocognitive sequelae, Byrne proposed the use of non-steroidal anti-inflammatory drugs (NSAIDs) as a means of combating this complication (Byrne 2005).

The third form of treatment of brain cancer is chemotherapy. A number of chemotherapeutic drugs, as well immunotherapy agents have been used for this condition. One of the first chemotherapeutic agents used for brain cancer was methotrexate (MTX). Newer agents used to treat certain forms of brain cancer include procarbazine, platinum analogs (cisplatin, carboplatin), the nitrosoureas, BCNU, and etoposide. Temozolomide, granulocyte-macrophage colony-stimulating factor, as well as rituximab are immunotherapeutic agents currently being investigated for the treatment of brain cancers. A problem with chemotherapy is that, due to the size of the molecule, there are few chemical agents that can cross the blood-brain barrier to get to the tumor. An additional concern with chemotherapy is that these agents work by interrupting mitosis, the process of cell division. By nature, many brain tumors grow slowly, so slowing tumor growth by these chemotherapy agents does not result in significant clinical improvement.

Some cancer cases are treated with chemotherapy after surgery and radiation. Chemotherapy can be used as a radio-sensitizing agent with radiation to control a recurrent tumor and to treat patients who can no longer tolerate radiation therapy. Studies have shown that some patients who receive chemotherapy for malignant tumors have improved survival rates compared to patients who do not, but the effectiveness of chemotherapy agents is limited and depends on the tumor type (Dinnes, Cave, Huang, Milne 2002; Kim, Lee, Yun, Kim, et al. 2005).

III. History of Medicare Coverage

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services). BBBD used as part of a treatment regimen for brain tumors is considered to be within the following benefit categories: inpatient hospital services (§1861 (b)), and physicians' services (§1861 (q)). This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Medicare does not currently have a National Coverage Determination for BBBD used as part of a treatment regimen for brain tumors.

IV. Timeline of Recent Activities

July 11, 2006

CMS accepted a formal request for non-coverage of BBBD used as part of a treatment regimen for brain tumors.

A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.

August 10, 2006	The initial 30 day public comment period ended. Thirty-nine comments were received.
December 27, 2006	CMS posted its Proposed Decision Memorandum and opened a 30 day public comment period.
January 26, 2007	The public comment period ended. Eleven comments were received.

V. FDA Status

Blood brain barrier disruption as a procedure is not regulated by the FDA. The individual chemotherapeutic agents and BBB disruption agents are FDA approved drugs and/or biologics. Mannitol does not have FDA approved labeling for disruption of the BBB. Mannitol (marketed as Osmitrol and generics) has labeled indications for the promotion of diuresis, in the prevention and/or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established; the reduction of intracranial pressure and treatment of cerebral edema by reducing brain mass; the reduction of elevated intraocular pressure when the pressure cannot be lowered by other means, and promoting the urinary excretion of toxic substances.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review. The evidence reviewed to date in this final decision memorandum includes the published medical literature on BBBD reviewed as part of our internal technology assessment as well as all articles and studies submitted during the two public comment periods.

B. Discussion of evidence reviewed

1. Question:

Is the evidence sufficient to conclude that blood brain barrier disruption, when used as part of a treatment regimen for brain tumors, improves patient-centered health outcomes in Medicare beneficiaries, compared to therapies that do not include blood brain barrier disruption?

2. External technology assessments

CMS did not commission an external technology assessment on this issue.

We are aware of a November 2001 technology assessment performed by the Institute for Clinical Systems Improvement (ICSI), entitled Blood Brain Barrier Disruption Chemotherapy. The committee noted the difficulty comparing results from different trials and that few patients with any given tumor type were studied. It called attention to the likelihood of selection bias. The committee summary included seven points, which are abstracted below:

- Long term effects of repeated BBBD procedures are unknown.
- BBBD used as part of a treatment regimen for brain tumors is acceptably safe when performed by experienced physicians in large, regional centers.
- Protocols using high dose methotrexate for PCNSL with or without BBBD consistently produced response rates > 75%. The use of BBBD may preclude the need for whole brain radiation therapy.
- Some patients with anaplastic astrocytoma or glioblastoma multiforme experience tumor shrinkage.
- For CNS germ cell tumors the relative efficacy compared to conventional chemotherapy is unknown.
- Response rates > 69% were seen for the few evaluable cases of primitive neuroectodermal tumor (PNET)/medulloblastoma.
- There are insufficient data on patients with metastatic disease to make a comparison to conventional chemotherapy.

(Accessed 12/13/06 athttp://www.icsi.org/knowledge/detail.asp?catID=107&itemID=268)

3. Internal technology assessments

CMS performed an extensive literature search utilizing PubMed for new randomized controlled trials (RCTs) and systematic reviews evaluating the use of BBBD used as part of a treatment regimen for brain tumors. The literature search was limited to the English language and specific to the human population.

Literature search

Due to the paucity of published information on this subject, most of the studies evaluating the use of blood brain barrier disruption in patients with brain tumors were supplied by those most familiar with the technique. This information was supplemented with additional information from MEDLINE, Cochrane Review, ECRI, NCI, as well as multiple oncology, medical and surgical textbooks. Peer-reviewed articles written in English were reviewed. Search terms included blood brain barrier disrupters, blood brain barrier opening, blood brain barrier modification, brain cancer (both primary and metastatic), primary CNS lymphoma, malignant brain tumors, and mannitol. We focused the review on original reports of the use of hyper-osmotic agents used as an adjunct to chemotherapeutic agents in the treatment of primary and metastatic brain cancer. We also reviewed original reports of the use of osmotic blood brain barrier disrupters.

A review of the literature has failed to reveal any published RCT results. A number of case studies, case series and nonrandomized controlled study designs have been published on the association between BBBD and the treatment of intracranial malignancy.

Evidence review

Early studies on the use of blood brain barrier disrupters

A number of original studies evaluated the feasibility of using osmotic agents as blood brain barrier disrupters to increase chemotherapeutic agents to the brain (Neuwelt, Frenkel, Diehl, Maravilla et al. 1980; Neuwelt EA 1980; Neuwelt, Specht, Howleson et al. 1983). Neuwelt and associates were among the first to study the reversibility of BBB disrupters in patients with malignant brain tumors (Neuwelt, Frenkel Diehl, Vu et al. 1980). In this case series, 5 subjects with gliomas or metastatic brain tumors (glioblastomas, anaplastic astrocytoma, metastatic breast cancer) were given mannitol infusions intracranially, followed by an intravenous contrast agent (technetium pertechnitate). The intervention resulted in good to excellent blood brain barrier disruption in 4 of 5 subjects. Two transient complications occurred in separate subjects (seizures and aphasia). And although a single non-transient complication occurred (a superficial wound infection at the burr hole site in 1 subject), reversible transient osmotic barrier disruption was achieved 15 times in five patients without additional toxicity. This study provided evidence that a metastatic or glioblastoma tumor could have a blood brain barrier intact to an intravenous contrast agent, which only becomes permeable to this contrast agent after osmotic disruption. In a later study, Roman-Goldstein and associates demonstrated that non-ionic iodine-based contrast medium was associated with a lower incidence of seizures when injected intravenously in conjunction with osmotic blood brain barrier disrupters, compared to ionic contrast media (Roman-Goldstein, Clunie, Stevens, et al. 1994). Based on this early study which used both primary as well as metastatic brain cancer, contrast enhanced CT is the preferred method to image disruption because it has better spatial resolution than radionuclide imaging techniques.

Another early study evaluated whether or not chemotherapy drug levels following BBBD are correlated with the degree of barrier disruption measured by CT scan and radionuclide scans. Neuwelt and associates performed one of the first studies to evaluate BBBD used as part of a treatment regimen in patients with malignant brain tumors (Neuwelt, Diehl, Vu, et al. 1981). In this case series, the authors monitored intra-carotid delivery of methotrexate (MTX) in six patients with malignant glial tumors who had received mannitol as an osmotic BBB disrupter. MTX was chosen during this initial trial because of its potential for low toxicity during direct exposure, its reported response in brain tumors, and the availability of a reliable assay method. During the study, a total of 33 disruptions occurred. Two subjects showed clinical improvement, one of whom had evidence of tumor regression by CT scan. No significant or permanent adverse neurologic or systemic sequelae occurred among participants. The neuroradiologic evaluation showed that MTX in the tumor persisted longer after BBB disruption than without disruption. This study also revealed that cerebrospinal fluid MTX levels were not a sensitive measure of the degree of barrier disruption as measured by either CT or brain scan.

Neuwelt and associates explored concurrent tumor regression in areas distant to barrier opening (Neuwelt, Hill, Frenkel 1984). This case series included 3 subjects, each with a distinct type of brain malignancy: metastatic breast cancer, glioblastoma, and PCNSL. They all had objective responses to combination chemotherapy in conjunction with BBB modification in those areas of the brain perfused. This was documented by serial CT studies confirming reduction in the size of the intracranial lesions, and physical examination that confirmed clinical improvement. The study also showed that osmotic BBB disruption increases drug delivery not only to the tumor but also to the surrounding brain area. Subsequent to the procedure, each patient developed the occurrence or recurrence of CNS disease in areas not directly perfused by the chemotherapeutic agent. The authors concluded that though drug resistance could partially explain treatment failures, another possible cause could be that drug delivery to the tumor could be seriously affected by a partially or completely intact BBB. This could explain tumor regression seen only in those areas of the brain undergoing BBB disruption.

The use of blood brain barrier disruption as part of therapy for brain tumors

A number of studies have been conducted using BBBD along with chemotherapy for the treatment of various types of brain malignancies, including primary disease. Neuwelt and associates, as well as other authors, have performed a number of case series studies evaluating the use of BBBD in patients with PCNSL of the brain (Neuwelt, Frenkel, Gumerlock, et al. 1986; Neuwelt, Goldman, Dahlborg, Crossen et al. 2000; Crossen, Goldman, Dahlborg, Neuwelt 1992; Dahlborg, Henner, Crossen, Tableman et al. 1996; Roman-Goldstein, Jones, Delashaw et al. 1998; McAllister, Doolittle Gustadisegni, Kraemer et al. 2000; Neuwelt, Goldman, Dahlborg et al. 1991; Kraemer, Fortin, Doolittle, et al. 2001; Tyson, Siegal, Doolittle, Lacy et al. 2003; Ferreri, Abrey, Blay, Borisch et al. 2003; Neuwelt, Guastadisegni, Varallyay et al. 2005; Abrey, Batchelor, Ferreri, Gospodarowicz et al. 2005). Other types of primary brain tumors that BBBD along with chemotherapy has been used for on include malignant glial tumors (Neuwelt, Diehl, Vu, et al. 1981), non-glial primary brain tumors (Dahlborg, Petrillo, Crossen, Roman-Goldstein et al. 1998); and glioblastomas (Neuwelt, Howieson, Frenkel, Specht et al. 1986; Hall, Doolittle, Daman, Bruns et al. 2005), and germinoma (Neuwelt, William, Mickey et al. 1994).

BBBD as part of a treatment regimen for brain tumors has also been used on a number of cancers metastatic to the brain. Some studies have evaluated individual tumor types such as melanoma (Neuwelt, Specht, Barnett, Dahlborg et al. 1987 as well as breast cancer (Tyson, Kraemer, Hunt, Muldoon, Orbay, et al. 2006). Other studies have evaluated the use of BBBD in the setting of both primary and secondary brain cancer (Neuwelt, Dahlborg 1987; Roman-Goldstein, Clunie, Stevens, Hogan, et al. 1994; Roman-Goldstein, Mitchell, Crossen, William et al. 1995; Williams, Henner, Roman-Goldstein, Dahlborg, et al. 1995).

We discuss the use of BBBD used as part of a treatment regimen for specific types of brain tumors below. The first section describes the evidence on primary intracranial malignancies, i.e. those malignancies arising in the brain whether or not the cell type is neural, glial, or other. The second section describes the evidence for metastatic malignancies, i.e. tumors that originated in other locations such as breast or skin.

Primary intracranial malignancies

Primary Central Nervous System Lymphoma

The literature has revealed a large number of studies evaluating the use of BBBD and chemotherapeutic agents for PCNSL. Neuwelt and associates were among the first to evaluate mannitol for BBBD in conjunction with MTX as well as other chemotherapeutic agents in the treatment of PCNSL (Neuwelt, Balaban, Diehl, et al. 1983). The first case involved a 37 year old subject with PCNSL treated with MTX, leucovorin rescue, procarbazine, and cyclophosphamide. He received nine courses of treatment with the above mentioned drugs. CT studies showed a decrease in tumor size with each treatment. Further CT studies showed no evidence of tumor before his eighth treatment. At the time of the publication, this subject had complete tumor regression and was neurologically intact. The second case involved a 60 year old with PCNSL who received MTX as well as cyclophosphamide. Despite the response after six treatments, the patient decided to discontinue treatments temporarily for geographic reasons, and was subsequently treated with radiation. Though complete tumor regression occurred, the subject died 12 months after diagnosis. The final case involved a 67 year old with PCNSL. The patient initially responded to cranial irradiation to the entire brain, but a few months later the tumor recurred. The patient then underwent BBB disruption and received intravenous cyclophosphamide, procarbazine along with MTX. During the course of therapy, the patient received two courses of treatment, and though the patient continued to have some bilateral leg weakness at the time of publication of the article (almost a year after getting first BBBD treatment), there was steady improvement and no evidence of tumor seen on enhanced CT.

Using a prospective series, Neuwelt and associates followed the course of 12 subjects with PCNSL to determine if a new approach to diagnosis (integrating the use of needle brain biopsy and immunochemical staining for monoclonal antibodies) and treatment (use of BBBD along with chemotherapy) was effective for this condition (Neuwelt, Frenkel, Gumerlock, Braziel et al. 1986). Baseline radiographic studies were obtained (e.g., CT scans, MRIs, radionuclide brain scans), as well as special laboratory studies (e.g., cytology, immunoassays, protein electrophoresis for immunoglobulins studies). BBBD was initiated along with combinations of cyclophosphamide, MTX, leucovorin rescue, and procarbazine. Sequential BBBD and concomitant drug therapy was repeated during the course of therapy. Subjects were followed for a median of 19 months (range, 12-48 months). Results of the study revealed that CT-guided needle biopsy contributed to the diagnosis in 6 patients, and immunochemical staining methods detected monoclonal antibodies in those tested. The study also reported an initial complete response in 75% of participants, and a 1-year survival rate of 75%. The author noted that the clinical response rate and survival rate were at least as effective as radiotherapy as a primary therapeutic modality for PCNSL.

Kraemer and associates explored the relationship between total dose intensity of chemotherapy delivered by BBBD in patients with PCNSL, and its relationship with survival (Kraemer, Fortin, Doolittle, Neuwelt 2001). This study involved the use of 74 patients with PCNSL who did not have systemic lymphoma or radiation treatment prior to initiation of BBBD followed by chemotherapy. Two chemotherapy protocols were used: MTX, cyclophosphamide, procarbazine (protocol 1) vs. MTX, cyclophosphamide, etoposide, and granulocyte colony stimulating factor (protocol 2). Baseline characteristics were used as potential exploratory variables (e.g., gender, age, protocol, number of disruptions, chemotherapeutic dosage intensity etc.) During this study of 74 patients, a total of 1047 BBBD procedures were performed, and total dose intensity of chemotherapy was estimated using the number of intra-arterial infusions, or a cumulative degree of BBBD score. The study revealed that survival was significantly associated with intensity of chemotherapy, i.e. increased dose intensity results in increased survival.

A number of other studies have also been performed which have evaluated BBBD used as part of a treatment regimen for brain tumors along with chemotherapy in patients with PCNSL, and have tried to determine if cognitive function was affected. Neuwelt and associates followed 2 groups of patients; 13 patients that received cranial irradiation 1 to 9 months before referral (group 1), and 17 patients who received initial BBBD and chemotherapy with subsequent radiation only for tumor progression or recurrence (group 2) (Neuwelt, Goldman, Dahlborg, Crossen, et al. 2000). For patients in group 2, mannitol was used for BBBD, in conjunction with cyclophosphamide, MTX, leucovorin rescue, and procarbazine as chemotherapeutic agents. A battery of neuropsychological test was used to assess cognitive function (e.g., Wechsler Memory Scale and Revision-WMS and WMS-R; Wechsler Adult Intelligence Scale-Revised-WMS-R; Trail Making Test: Parts A and B-TMT, Karnofsky performance scores etc.), and characteristics of subjects were compared to 208 PCNSL patients abstracted from 15 published series (historical control). The results of the study revealed that the median survival for group 1 (cranial irradiation) was 17.8 months, comparable with the 20 month median survival of the historical control series. The median survival for group 2 (BBBD followed by chemotherapy) was 44.5 months. The authors also noted that improved survival was associated with preservation of cognitive function in six of seven non-irradiated complete responders observed over a 7 year period, while for those that received irradiation, several patients maintained average test results.

Crossen and associates also explored whether or not cognitive function is affected in patients with PCNSL after receiving BBBD and chemotherapy (MTX, Cytoxan, procarbazine) (Crossen, Goldman, Dahlborg, Neuwalt, 1992). This study followed for 7 years 8 consecutive patients with PCNSL who received BBBD and chemotherapy. Baseline neuropsychological testing (e.g., WAIS-R, WMS-R, CFT, VLT, TMT-B) as well as Karnofsky Performance Scores (KPS) were obtained. Results of the study revealed that 7 of the 8 participants had full-scale intelligence quotient scores which tended to remain stable, as did learning performance, memory scores, and other neurobehavioral variables. Trends of summary neuropsychological test indices were stable or improved for this group. Only one participant had lower test scores compared to baseline scores that was greater than one standard deviation on 3 variables.

Dahlborg and associates studied patients with and without antecedent cranial irradiation to determine if cognitive function is affected (Dahlborg, Henner, Crossen, Tableman, Petrillo et al. 1996). Fifty eight consecutive patients with PCNSL were subdivided into 2 groups: group 1-those referred to medical center at tumor progression or recurrence and after initial cranial radiation (n=19), and group 2 - those referred after initial diagnosis, not receiving cranial irradiation (n=39). Subjects ages' ranged from 5 to 71, with 34% over age 60. Extensive clinical, neurological, ophthalmologic and neuropsychological testing was performed as well as radiological testing and KPS. Baseline demographic characteristics, as well as serial neuropsychological evaluation were also performed. Characteristics of a group of historical controls were extracted from the medical literature. Mannitol was used as the BBBD and MTX, leucovorin rescue, cyclophosphamide, and procarbazine were used as chemotherapeutic agents. The study revealed that the median survival from date of first BBBD for group 1 patients was 8.5 months, and for the group 2 patients 40 months, but with the small sample size the difference did not reach statistical significance ($p<0.06$). In the neuropsychological evaluation (patients were followed for 7 years), none of the patients who received only chemotherapy with BBBD and who did not receive radiation therapy suffered significant global decline in neuropsychological test results. Three of eight patients who received cranial radiation suffered declines in neuropsychological testing. This study demonstrated that for patients with PCNSL, receiving BBBD and chemotherapy preserved or improved cognitive function can be achieved, compared to PCNSL patients treated with cranial irradiation.

Exploring the association between cognitive outcomes and the use of BBBD followed by chemotherapy, McAllister and associates followed a cohort of PCNSL patients after treatment (McAllister, Doolittle, Guastadisegni, Kraemer, Lacy, et al. 2000). The study consisted of 74 patients with PCNSL who had no systemic lymphoma or who had not received cranial irradiation, and who had undergone the first BBBD therapy at least 6 months prior to this study. During this study, there were 2 BBBD-enhanced chemotherapy protocols used: MTX, etoposide or cyclophosphamide, procarbazine, leucovorin rescue (protocol 1) or MTX, etoposide, cyclophosphamide, granulocyte colony stimulating hormone, leucovorin rescue (protocol 2). A battery of neuropsychological testing was performed at baseline and follow up studies were later performed (e.g., FSIQ, GMI, DRI, TMTB, etc). Other demographic characteristics and KPS were obtained at baseline. The results of the study revealed that the estimated 5-year survival rate was 42% for this group, and the median survival time was 40.7 months. Complete remission occurred in 48 patients (65%), and 36 patients continued to show complete remission response after 1 year of BBBD used as part of a treatment regimen for brain tumors followed by chemotherapy. Of these 36 patients, none demonstrated any evidence of cognitive loss.

Studies have also been done to determine responses for patients with relapsed PCNSL treated with second-line BBBD followed by chemotherapy. Tyson and associates followed 37 relapsed patients with PCNSL previously treated with first-line therapy of MTX-based chemotherapy (Tyson, Siegal, Doolittle, Lacy, Kraemer et al. 2003). Patients ranged in age from 22 to 77 (mean age 57.5); all (except 1) were treated within 8 months after relapse, and 9 subjects had had previous radiotherapy. BBBD followed by chemotherapy consisted of mannitol as the BBBD, and carboplatin, etoposide, cyclophosphamide (either alone or in combination) were used as chemotherapy agents. Definitions of disease progression as well as survival were provided. Neuropsychological testing was performed at baseline as well as at completion of the study if subjects had complete response at 1 year after starting carboplatin, and patient characteristics were noted (e.g., gender, age, KPS, radiographic tumor response, survival). The results of the study revealed that the median time for survival after BBBD followed by chemotherapy was 6.8 months; however, 18% of patients survived $\geq$ 27 months, 24% had complete radiographic response, 11% had partial radiographic response, 32% had stable disease, and 27% had progressive disease. The median time to failure for patients with complete response and partial response was 9.1 months. A neuropsychological evaluation was performed on 4 of 8 subjects with complete response. Of these patients, there were no neurocognitive alterations in one patient, and a significant improvement in another patient who was diagnosed 11 years prior and was disease-free at the end of the study. Of the other two, one developed a systemic disease and was too ill to perform the post BBBD testing, and the other was in a stupor prior to treatment with BBBD, but completed post BBBD neuropsychological testing. No further information was given about the results. The authors concluded that for patients with relapsing PCNSL, intra-arterial chemotherapy with BBBD is a potential treatment alternative.

In a separate study, Neuwalt and associates were again able to demonstrate, that for PCNSL patients receiving enhanced chemotherapy, neither enhanced chemotherapy delivery nor changes on MRI imaging following therapy were associated with decreases in cognitive function (Neuwelt, Guastadisegni, Varallyay, Doolittle 2005).

Glioblastoma

Neuwelt and colleagues also evaluated the use of BBBD when used as part of a treatment regimen for brain tumors in patients with glioblastoma (Neuwelt, Howieson, Frenkel, Specht et al. 1986). In this 3-arm study, 38 patients with glioblastoma (experimental group) previously treated with surgery and cranial radiation were compared to 2 historical control groups of patients with glioblastoma: one group had 14 patients treated with surgery and radiation (group 1), and the second group consisted of 8 patients with surgery, radiation, and systemic chemotherapy (group 2). Functional performance status based on KPS was measured at baseline for participants. Subjects in the experimental group received mannitol for BBBD, and cyclophosphamide, MTX, procarbazine and leucovorin rescue as chemotherapy agents. Cox Proportional Hazard was used in determining survival time, the primary outcome of interest. Risk factor effects of age, functional status, treatment, and tumor necrosis upon expected survival time were also examined. The study demonstrated an inverse relationship between age and survival time and a positive correlation between functional status and survival time (i.e. younger more functional patients given BBBD followed by chemotherapy had significantly prolonged survival compared to older patients). No significant effects upon survival time in the 3 groups were demonstrated for tumor necrosis. The median survival was 12.8 months for the group 1 controls, and 11.4 months for the group 2 controls, and 17.5 months for the experimental. This survival advantage was associated with a median KPS of 65% for those patients surviving 24 months. Neurologic as well as non-neurologic complications were reported for the experimental group (but not reported for the historical controls).

Malignant glial tumors

Neuwelt and associates evaluated the use of BBBD when used as part of a treatment regimen for brain tumors in patients with malignant glial tumors (Neuwelt, Diehl, Vu, et al. 1981). In this study, 6 of 8 participants had a malignant glial tumor, the other 2 patients had metastatic tumor in the brain. All subjects were treated with BBBD/MTX. The authors note that 6 patients who received BBBD followed by chemotherapy had a total of 33 disruptions. Also noted by the authors is the fact that 2 patients showed clinical improvement, one of whom had evidence of tumor regression by CT scan.

Non-glial primary brain tumors

Dahlborg and associates also evaluated the use of BBBD when used as part of a treatment regimen for brain tumors in patients with non-glial primary tumors (Dahlborg, Petrillo. Crossen, Roman-Goldstein et al. 1998). Thirty-four patients with histologically confirmed germ cell tumor (n=9), PCNSL (n=9), or primitive neuroectodermal tumor (n=16) were included in the study. Participant's ages ranged from 1 to 30. Prior treatments included surgery and chemotherapy. Baseline neuropsychological testing was performed, as well as clinical evaluation. Two combination chemotherapies were used: MTX, cyclophosphamide, procarbazine, and etoposide (protocol 1), or carboplatin, etoposide, and cyclophosphamide (protocol 2). During the study, 645 BBBD and chemotherapy sessions were performed and no mortalities occurred. After treatment, of the 34 subjects included in this study, 82% had an objective response to treatment (62% with complete response, 20% with partial response). Ototoxicity was a common complication noted in patients using protocol 2 (62%). The authors note that for most patients, cognitive functioning was maintained or improved at follow up, but also notes that sample size of groups of patients with different radiation status were too small for statistical comparison.

Pontine glioma

Hall and colleagues evaluated the use of BBBD when used as part of a treatment regimen for brain tumors in patients with diffuse pontine gliomas (Hall, Doolittle, Daman, Bruns, et al. 2005). This study involved 8 patients with diffuse pontine gliomas, ranging in age from 2 to 44. All patients had at least 2 cycles of BBBD followed by chemotherapy and 19 was the maximum number of cycles. Chemotherapeutic agents used in the study included MTX, cyclophosphamide, etoposide, or carboplatin, cyclophosphamide and etoposide. After treatment, MR imaging revealed partial response in 2 patients, stable disease in 5, and progression of disease in one. The median time to tumor progression was 15 months (ranging from <1 month to 40 months). The median survival form the first BBBD treatment was 16.5 months (ranging from 5 to 59 months).

Germinoma

Disseminated primary intra-cranial germinoma has been treated with both surgery as well as radiation. But due to mixed survival results, Neuwelt and associates used platinum-based chemotherapy delivery with osmotic blood brain barrier disruption to determine if survival could be improved upon (Neuwelt, William, Mickey, Frenkel, Henner 1994). This study consisted of 4 consecutive patients known to have a poor prognosis due to tumors located in more than one anatomic location. Participants ranged in age from 14 to 29 years. All patients received chemotherapy in a 2-stage regimen. Patients received initial treatment with cisplatin and etoposide, then consolidation therapy consisting of etoposide with carboplatin in conjunction with BBBD. Paired BBBD followed by chemotherapy infusions were administered sequentially with mannitol. The study noted complete response in all 4 subjects, and at the time of publication, three participants were tumor-free without radiotherapy 24 to 40 months from diagnosis. The 3 patients who remained tumor-free did not develop cognitive deterioration, but all developed high-frequency hearing loss.

Studies involving a mixture of primary brain tumors

Studies evaluating whether or not cognitive function was affected by BBBD when used as part of a treatment regimen for brain tumors have also been performed on patients with a mixture of primary brain tumors. Roman-Goldstein and associates evaluated 15 consecutive patients with metastasis to the brain (Roman-Goldstein, Mitchell, Crossen, Williams, et al. 1995). Patients involved in the study had PCNSL, germinomas, astrocytomas, or neuroectodermal tumor. Subjects' ages ranged from 6 to 66. Before and after 1 year of treatment with BBBD followed by chemotherapy, all patients underwent MR imaging and a battery of neuropsychological testing (e.g., Wechsler Adult Intelligence Scale-Revised, Trail making test-parts A and B, Rey-Osterreith Complex Figure test, etc). Two different chemotherapy regimens were used: cyclophosphamide, MTX, and procarbazine or etoposide and carboplatin. A total of 318 BBBD procedures were performed on participants. The results of the study revealed that 10 patients (67%) had no new abnormalities on repeat MR imaging, while recurrent tumor occurred in 5 patients (33%). No patient showed a decline in global cognitive function, and 5 patients showed improved global scores. There were a few patients who showed decreases on certain neuropsychologic test, but these were rare and did not suggest a pattern of selective impairment on any individual neuropsychological function.

Metastatic malignancies

A number of studies have evaluated the use of BBBD when used as part of a treatment regimen for brain tumors in metastatic disease to the brain. These tumors include: malignant melanoma (Neuwelt, Specht, Barnett, Dahlborg, et al. 1987) and breast cancer (Tyson, Kraemer, Hunt, Muldoon, et al. 2006). A number of studies have been done which use BBBD along with chemotherapy for a number of different types of metastatic tumors within the same study (Neuwelt, Dahlborg 1987; Roman-Goldstein, Clunie, Stevens et al. 1994; Roman-Goldstein, Mitchell, Crossen, Williams et al. 1995; Williams, Henner, Roman-Goldstein, Brummett, et al. 1995; Doolittle, Miner, Hall, Seiger, Hansom, et al. 2000; Doolittle, Anderson, Bleyer, Cairncross, Cloughesy, Eck, et al. 2001).

Melanoma

Tumor-specific monoclonal antibodies have been used in the treatment of metastatic disease to the brain. Neuwelt and associates have used this modality in conjunction with BBBD for the treatment of melanoma (Neuwelt, Specht, Barnett, Dahlborg, et al. 1987). This study involved 3 patients with malignant melanoma metastatic to the brain confirmed by CT and MR imaging. Baseline studies including tumor samples, KPS, blood studies including immunoperoxidase staining, dosimetric measurements, radionuclide scanning, immunohistochemical testing of samples, and other tests were performed. Tumor samples demonstrated excellent immunohistochemical reactivity to Fab 96.5 (specific for melanoma antigen) or Fab 48.7 (specific for a melanoma-associated proteoglycan antigen). Typically, the overall study design consisted of a 3-week protocol: week 1-iodinated anti-melanoma nonspecific Fab 48.7 or 96.5; week 2-the infusion of Fab 1.4 (an iodinated nonspecific antibody); week 3-iodinated Fab 48.7 or 96.5 after osmotic opening with BBBD. Anterior and posterior images of the head, neck, and trunk were taken after administration of Fab. Cerebral perfusion was then estimated. The study revealed that there was no uptake of either antibody into the region of the tumor (as documented by brain imaging) though the authors gave no time table of this occurrence; however, there was increased uptake in the blood brain barrier disrupted areas in all three subjects when radiolabeled tumor-specific Mab (antibodies directed to antigens on melanoma) was administered in conjunction with osmotic BBB opening. Serial brain scans showed that >90% of the radiolabeled antibody cleared from the brain by 72 hours.

Breast cancer

Though therapeutic options for the treatment of metastatic systemic brain tumors for breast cancer have improved, median survival is only 3 to 12 months with current standard therapy of whole-brain radiotherapy, surgery, and stereotactic radiosurgery. Tumor-specific monoclonal antibodies, in conjunction with BBBD, have also been used for the treatment of metastatic disease from the breast. Tyson and colleagues performed a retrospective analysis involving 25 patients diagnosed with central nervous system breast cancer metastases between 1981 and 2004 to determine if chemotherapy and immunotherapy using trastuzumab would be more effective against brain metastasis (Tyson, Kraemer, Hunt, Muldoon, Orbay, et al. 2006). Ages ranged from 25 to 65. Ten subjects had metastasis only to the brain, while the other 15 had brain and systemic involvement. Baseline characteristics were obtained. In this study patients received a variety of therapies some of which included BBBD. We were not able to determine from the report which specific therapies were associated with which specific outcomes. Chemotherapy consisted of MTX, cyclophosphamide and etoposide. Ten patients were treated with this regimen. After 1994, IA carboplatin was substituted for MTX in patients receiving BBB disruption therapy. A total of 7 patients received trastuzumab (of these 7, six received carboplatin-based chemotherapy and one received MTX-based chemotherapy). Of the seven patients who received trastuzumab, two subjects had BBB disruption therapy, 3 subjects received only IA therapy, and 2 subjects received both IA and BBB disruption therapy. A total of 215 BBB disruption procedures were performed. Treatment was well tolerated by most patients. The results of the study revealed that the median overall survival of the cohort was 45.5 weeks. Of those patients evaluable for response, 4 had objective responses (either complete or partial) for a response rate of 16%, 15 had stable disease (60%), while the other 6 had progressive disease (24%). Median time to progression was 4.13 months, the 6 month progression-free survival was 32% and the 12-month progression-free survival was 12%. The authors noted that in general, BBB disruption therapy was well tolerated; they also noted that when comparing the 7 patients that received trastuzumab to the 18 patients that did not, response and survival could not be assessed.

BBBD followed by chemotherapy use in the setting of both primary and secondary brain cancer

One of the first studies that evaluated the use of BBBD followed by chemotherapy involved a case series of patients with metastatic disease to the brain. Neuwelt and associates presented information on 3 cases involving patients with glioblastoma, metastatic breast disease, and PCNSL (Neuwelt, Hill, Frenkel 1984). This was one of the early feasibility studies, and can be reviewed in the section on the early use of BBBD; it showed that patients with differing types of brain malignancies could respond to combination BBBD followed by chemotherapy. It also showed that osmotic BBB modification increases drug delivery not only to the tumor but also to the surrounding brain area.

Neuwelt and Dahlborg studied the use of BBBD when used as part of a treatment regimen for brain tumors in metastatic brain cancers from differing organs (Neuwelt, Dahlborg 1987). Seven patients with intra-cranial metastasis underwent a total of 36 osmotic blood brain barrier modification procedures. Patients ranged in age from 24 to 65. Cancer included the following: breast cancer, lung cancer, CNS lymphomas, testicular cancer, and small cell lung cancer. BBBD (mannitol) was used in combination with MTX, procarbazine, and Cytoxan. Based on follow up radionuclide studies, good to excellent disruption was documented in 50% of procedures, and in only 3 procedures (8%) was there no evidence of disruption. Complications during the procedure included seizures, febrile granulocytopenia, and anemia. The authors noted that though this was a small study, the results indicate that barrier modification can be carried out in patients with central nervous system (CNS) metastasis with minimal toxicity, and suggest that blood brain barrier disruption can increase drug delivery to both tumor and surrounding brain resulting in an objective clinical response.

Another study which used a mixture of primary and secondary brain malignancies to evaluate the effectiveness of BBBD when used as part of a treatment regimen for brain tumors was performed by Williams and associates (Williams, Henner, Roman-Goldstein, Dahlborg, Brummett, et al. 1995). In this efficacy study, 34 patients with a number of different types of cancers of the brain (glioblastoma multiforme, malignant astrocytoma, malignant astrocytoma-oligodendroglioma, primitive neuroectodermal tumor, disseminated CNS germ cell tumor, PCNSL, metastatic breast cancer, metastatic lung cancer) were followed after BBBD followed by chemotherapy treatment. Patient's ages ranged from 7 to 72. Some patients had received no prior radiation or chemotherapy (n=11), some patients had received prior cranial radiation (n=13), and some patients had received prior BBBD with MTX and Cytoxan (n=11). Mannitol was used for BBBD in conjunction with etoposide and carboplatin. Baseline demographic studies were obtained, along with clinical, neuropsychological testing, and radiographic studies. A total of 311 BBBD procedures were performed. Results of the study revealed that of the 34 patients included in the study, 22 had measurable disease and 9 radiographic responses (50% or more decrease in enhancing tumor) were noted in this group. Twelve patients were not evaluable. Though myelosuppression as well as high-frequency hearing loss were noted as complications in this study, complete responses were noted in all patients with primitive neuroectodermal tumors, as well as PCNSL, and partial to complete response was noted in patients with malignant astrocytoma. Other tumors (e.g., glioblastoma multiforme, metastatic breast/lung) showed no improvement. The authors felt that BBBD with carboplatin/etoposide was an effective treatment for some intracranial cancers.

One final study which evaluated BBBD when used as part of a treatment regimen for brain tumors in patients with both primary and secondary brain cancer was a multi-center study conducted by Doolittle and associates (Doolittle, Miner, Hall, Siegal, Hanson, et al. 2000). This study involved 221 patients from 5 university centers that had received 2646 BBBD procedures. Patients had either primary brain cancers (PCNSL, germ tumors, primitive neuroectodermal tumors, brainstem gliomas, glioblastoma multiforme, oligodendrogliomas, astrocytomas), or metastatic tumors (e.g., breast cancer). Radiographic studies (e.g., CT brain scans, MR imaging), KPS, clinical status, neuropsychologic testing were performed, and information on gender, age, number of patients previously treated with chemotherapy and/or radiotherapy were also collected. Depending on type of tumor involved, 2 different chemotherapy regimens were used: carboplatin, cyclophosphamide, etoposide (protocol 1), or MTX, cyclophosphamide, etoposide, leucovorin rescue (protocol 2). Both regimens used mannitol for BBBD, and granulocyte-colony stimulating factor. Patients ranged in age from 18 to 75. The results of the study revealed that, of the evaluable patients with PCNSL, 75% achieved complete response. All evaluable patients with primary neuroectodermal tumor (n=17), metastatic disease (n=12), or germ cell tumor (n=4) achieved stable disease or better. Of the 57 evaluable patients with glioblastoma multiforme, 79% achieved stable disease or better. Asymptomatic subintimal tears, pulmonary emboli, as well as renal toxicity were rare complications noted during the study. Based on the findings, the authors felt that for patients with chemotherapy sensitive tumors, enhanced delivery results in a high degree of tumor response, with an efficacy profile that is reproducible across multiple centers.

4. Medicare Evidence Development and Coverage Advisory Committee (MedCAC)

A MedCAC meeting was not convened on this issue.

5. Evidence-based guidelines

We found no evidence-based guidelines for the treatment of brain tumors using BBBD as part of a treatment regimen for brain tumors in a 12/13/06 search of www.guideline.gov.

6. Professional society position statements

The American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) Section on Tumors have discussed the issue of Medicare coverage of blood-brain barrier disruption and has adopted the following policy statement:

"The intra-arterial delivery of chemotherapy, with or without blood-brain barrier disruption, for the purpose of treating lymphoma is a recognized delivery procedure and is not, in itself, experimental."

The Oregon Medical Association submitted a public comment in support of coverage for BBBD followed by chemotherapy.

The Alliance of Dedicated Cancer Centers (ADCC) submitted a statement opposing the proposed noncoverage decision. ADCC disagrees with CMS on the significance of the absence of randomized clinical trials, proposes that the MCAC (now MedCAC) be convened on the subject of BBBD, and recommends that CMS allow coverage with ongoing evidence development.

7. Expert opinion

On August 10th, 2006, Dr Edward Neuwelt, who directs BBBD treatment and research at Oregon Health Sciences University (OHSU), reviewed his experience with BBBD during a meeting with the CAG staff at the CMS Central Office in Baltimore. He described the international BBBD consortium and its research and data collection efforts to date. Based on his research and the activities of the network, he opined that BBBD and subsequent intra-arterial chemotherapy were beneficial compared to alternative treatments in selected patients with chemosensitive primary and metastatic brain tumors.

8. Public comments

CMS received 39 comments during the initial public comment period, which were discussed in our proposed decision memorandum.

CMS received a total of 11 comments during the 30-day public comment period following publication of the proposed decision memorandum, of which, six comments (55%) were from physicians; two comments (18%) were from physician practice groups; one comment (9%) was from a nurse; one comment (9%) was from a professional organization; and one comment (9%) was from an insurer. One commenter (9%) provided additional references for review (these articles are discussed in the Evidence section). Six commenters (55%) also submitted comments during the first public comment period.

Of the six physicians who commented, three (50%) supported non-coverage of BBBD for any brain tumor, two (33%) supported coverage of BBBD only for PCNSL, and one (17%) supported coverage of PCNSL in the context of coverage with evidence development. Also, one professional organization, the Oregon Medical Association, commented in favor of coverage of BBBD for PCNSL in the context of coverage with evidence development.

Coverage for PCNSL
Four commenters (36%) indicated that they support coverage of BBBD only for primary CNS lymphoma (PCNSL) because available data show prolonged survival of BBBD-treated patients with decreased risk of cognitive deficits compared to patients treated with radiation therapy. One commenter suggested that randomized controlled trials are not essential.

Response:
Although the medical literature appears to be suggestive about the effectiveness of BBBD for the treatment of PCNSL, we believe these findings are attributable to deficiencies and inherent weaknesses in this type of evidence rather than the actual effectiveness of BBBD treatment. We cannot conclude that BBBD is beneficial because the available evidence is significantly limited by methodologic weaknesses such as lack of randomization, lack of concurrent controls during the investigation, small numbers of subjects and incomplete descriptions of the interventions. Though historical controls were used in the assessment, a number of confounders could exist which could have altered the relationship between tumor and intervention agent. We are not aware that these weaknesses have been adequately addressed by any published adjustment for these confounders.

Coverage with evidence development (CED) for PCNSL
Two commenters (18%) indicated that they support coverage of PCNSL in the setting of CED because observational data appear promising and randomized controlled trials are not a practical method of gathering data because of the rarity of this tumor type.

Response:

We believe it would be premature to use the Coverage with Study Protection (CSP) form of CED for osmotic BBBD at this time, given that CMS is currently reconsidering the current Clinical Trial Policy to, among other things, "clarify how items/services that do not meet the requirements of 1862(a)(1)(A), but are a potential benefit can be covered in clinical research studies as an outcome of the NCD process," and to clarify whether "an item or service non-covered nationally may be covered in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries." CMS initiated the reconsideration on July 10, 2006 and convened a [MedCAC] meeting on December 13, 2006. A proposed decision memorandum is expected to be issued on April 10, 2007. See the NCA Tracking Sheet for Clinical Trial Policy (CAG-0071R), available at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=186.

In addition, the current Guidance on CED also makes reference to the fact that the Clinical Trial Policy will be revised and that certain conditions of CED will be outlined and specified in the revised version. See Guidance for the Public, Industry, and CMS Staff - "National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development" (Document Issued on July 12, 2006).

In particular, the CED policy requires that coverage with CSP research conform to standards that will be developed by the Clinical Research Policy, and that "CMS will only provide payment for clinical research that meets the standards of a qualified trial as will be outlined in the revision of the Clinical Trial Policy." Given that the Clinical Trial Policy has not been finalized and that it has not yet been determined how this will affect NCDs involving CED-CSP, we believe that CED-CSP for osmotic BBBD is untimely. Of course, we may reconsider this national coverage determination for BBBD once the new clinical research policy is effective

Nonetheless we encourage the conduct of more rigorous clinical trials that could help establish whether chemotherapy administered after blood brain barrier disruption does indeed result in better health outcomes for patients with PCNSL and other brain cancers, though we point out that under the current clinical trial policy, Medicare can not pay for the investigational item.

Support of Non-coverage
Three commenters (27%) indicated that they support non-coverage of BBBD for any brain tumor type because the treatment modality remains unproven and the data available to date are insufficient to support administration of BBBD outside of a clinical trial. There should not be payment until the treatment is proven to be beneficial.

Response:
This comment supports CMS' decision to establish national non-coverage of BBBD.

Coverage for any brain tumor type
One commenter (9%) indicated that she supports coverage of BBBD regardless of brain tumor type. The commenter states that the BBBD procedure is safe when performed by specially trained physicians and that the data have shown decreased mortality and less risk of cognitive deficits as compared to brain irradiation. The commenter expressed the belief that we should provide all options to patients who suffer from brain tumors.

Response:
The available evidence is even sparser for brain tumors other than PCNSL. Though there were more medical studies which evaluated brain tumors other than PCNSL, the number of participants in these studies was smaller than in the studies involving patients with PCNSL. Because of the small sample size, it is difficult to attribute improved survival to BBBD in other tumor types. Hence, the evidence neither supports coverage of BBBD in PCNSL nor other types of brain tumors.

Implications of non-coverage policy
One commenter (9%) discussed the potential implications of the proposed non-coverage policy. He commented that the proposed decision would have a minimal effect on payment for BBBD.

Response:
We agree that the practical effect of this NCD in an inpatient hospital setting may be minimal due to the prospective bundled payment system used in that setting.

MedCAC
ADCC recommended that we convene the MedCAC on this topic.

Response:
We do not believe that the MedCAC should be convened on this topic at this time. The commenters have not materially disagreed with our summary of the evidence. Indeed there appears to be agreement even from proponents of BBBD about the quality and quantity of the available evidence. We believe that we have appropriately received expert input and that we have not missed relevant evidence. Rather, the contention regarding this NCA turns on the most appropriate CMS action pursuant to the available evidence, which we do not believe supports coverage of BBBD. As we note in other parts of this memorandum, our actions are determined by relevant statute, regulation and existing policy. The final decision clearly rests with CMS, and we do not believe that convening the MedCAC would be helpful in this instance.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, must not be otherwise excluded from coverage, and must be reasonable and necessary as defined in § 1862(a)(1)(A).

Question

Is the evidence sufficient to conclude that blood brain barrier disruption when used as part of a treatment regimen for brain tumors, improves patient -centered health outcomes in Medicare beneficiaries, compared to therapies that do not include blood brain barrier disruption?

Although our analysis must for clarity include discussion of the anticancer chemotherapy drugs that are administered after disruption of the blood brain barrier, we are not making a determination here about the reasonableness and necessity of anticancer drugs and biologicals for the treatment of brain tumors. We do note that the anticancer chemotherapeutic drugs and/or biologicals that are reported in the medical literature that was reviewed for this memorandum are FDA approved drugs, and that most of them are favorably cited for the treatment of one or more brain malignancies in one or both of the compendia listed in Section 1861(t)(2)(B)(ii)(I) of the Social Security Act. These citations do not mention the use of blood brain barrier disruption as part of a treatment regimen for brain tumors. Mannitol does not have a compendia listing for blood brain barrier disruption.

None of the available published studies which evaluated BBBD used as part of a treatment regimen for brain tumors were randomized controlled trials (RCTs). Most of the studies were case studies or case series. There were some controlled trials as well as prospective studies also included in the analysis. One reason given why no RCTs were available for this therapy was the rarity of the specific conditions, i.e. types of brain tumors, for which it is used. Others have claimed that it would be unethical to withhold therapy for patients with these diagnoses.

A large number of articles dealt with the use of BBBD when part of a treatment regimen for brain tumors in the setting of PCNSL. Though the outcomes seem promising, these studies also had a number of limitations, which included small numbers of cases as well as the lack of adequate controls and randomization. These limitations were common among most of the studies reviewed. Other limitations included that the findings could not be generalized to the Medicare population either because ages of participants were not reported in the study (Neuwelt, Specht, Barnett, Dahlborg, et al. 1987), or because study participants were not Medicare aged (Dahlborg, Petrillo, Crossen, Roman-Goldstein et al. 1998; Hall, Doolittle, Daman, Bruns, et al. 2005; Neuwelt, William, Mickey, Frenkel, Henner 1994; Doolittle, Miner, Hall, Siegal, Hanson, et al. 2000). Since the number of centers that can perform this procedure is severely limited, it would be hard to generalize the reported results to the practicing oncology community at large. In one of the controlled studies (Dahlborg, Henner, Crossen, Tableman, Petrillo et al.; 1996), no attempt was made to account for demographic differences between both study groups.

While the ICSI felt that BBBD is acceptably safe when performed by experienced physicians in large, regional centers, this evidence is derived from the experience of a very small number of specialized centers with very experienced practitioners. However, our reasonable and necessary standard is not confined to "acceptably safe." Our task is to determine that an item or service is or is not "reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member." Other organizations may, as appropriate to their missions, consider or weigh other criteria. We do not have adequate evidence to conclude that a similar safety profile would be attainable in other locations or when provided by less experienced practitioners.

The conclusions from many of the articles reviewed in this decision memorandum as well as public comments suggest that the protocol-directed use of BBBD when part of a treatment regimen for brain tumors in specialized treatment centers may have a limited role in certain types of brain tumors, specifically PCNSL. However, the methodologic shortcomings of the published reports prevent us from determining that BBBD used as part of a treatment regimen for brain tumors improves health outcomes in Medicare beneficiaries. Thus, at this time the evidence is insufficient to make a broad determination that the use of BBBD used as part of a treatment regimen for brain tumors in Medicare beneficiaries who have brain cancer is reasonable and necessary under Section 1862(a)(1)(A) of the Social Security Act.

Additional articles were sent in for review pursuant to the second public comment period. Some were peer-reviewed and published, while others are currently under review for publication. Articles submitted included literature reviews, systematic reviews, case studies as well as clinical trials. Limitations of the above mentioned articles include small sample sizes, lack of a control group or historical cohort for comparison, as well as insufficient representation of Medicare-eligible participants in the studies. These same limitations were found in the original set of articles reviewed. Our detailed analysis of the peer-reviewed published articles is presented below.

One published review article looked at pre-clinical and clinical trials involving the use of BBBD with chemotherapy in patients with PCNSL (clinical trials included in this newly submitted review article have already been discussed in the evidence section and are not repeated here) (Jahnke, Doolittle, Muldoon, Neuwelt 2006).

Another study looked at medical records and tumor specimens and evaluated the frequency, pathologic features, clinical data and the natural history of PCNSL (Miller, Hochbert, Harris, Gruber et al. 1994). Though the article did document that PCNSL had increased in frequency in the non-immunocompromised population, and that intermediate-grade histological types of PCNSL were decreasing over a thirty-year period, the article provided no information about medical management, including the use of BBBD therapy.

Fortin et al. performed a prospective trial which followed 38 patients with cerebral metastasis (Fortin, Gendron, Boudrias, Garant 2006). Primary tumors included ovarian carcinoma, breast cancer, small cell lung cancer, lung adenocarcinoma and systemic lymphoma. Intra-arterial carboplatin or methotrexate was used as chemotherapy, and BBBD was used only in the presence of a significant mass effect. According to the author, the results of the study revealed that patients had favorable outcomes. However, the author did not explain what these favorable outcomes were. The small number of participants in the study is a significant weakness that prevents us from determining that the intervention was indeed effective.

This conclusion does not affect the use of anticancer chemotherapy for brain tumors. Section 30 of the Medicare Benefit Policy Manual (Pub 100-02) states that a hospital stay solely for the purposes of use of a drug or biological that is determined not reasonable and necessary is not covered. If a beneficiary is admitted solely for the purpose of BBBD prior to anticancer chemotherapy, then the admission would not be covered. Those beneficiaries would typically receive their anticancer chemotherapy on an outpatient basis. If a beneficiary with a brain tumor is hospitalized for other reasonable and necessary reasons and during the hospitalization receives anticancer chemotherapy preceded by BBBD, only the BBBD would be noncovered.

We believe that robust clinical studies that include Medicare beneficiaries are needed to identify which patients may benefit from BBBD used as part of a treatment regimen for brain tumors. Public comment has noted the historical barriers to conducting such studies. We believe that Medicare support for such studies may be accomplished through our Clinical Trials policy. The Clinical Trial Policy provides an opportunity for payment of some clinical costs in a qualifying trial. See the Medicare NCD for Routine Costs in Clinical Trials (310.1), Medicare NCDs Manual, section 310.1, for a greater description of which costs would be covered.

We believe that a good clinical study should ideally:

- be registered at ClinicalTrials.gov;
- meet all the qualifying standards described under the Clinical Trial (Research) Policy;
- have a sample that ensures adequate representation of Medicare beneficiaries with brain cancer so that inferences may be readily generalized to the Medicare population;
- be designed to compare BBBD administered in conjunction with anticancer chemotherapy against active therapies that would otherwise be administered;
- have primary and secondary outcomes that reflect clinically significant patient centered health outcomes;
- enroll subjects in facilities that are capable of providing comprehensive cancer care; and
- use chemotherapeutic agents that are FDA labeled or favorably cited in the statutorily accepted compendia for the treatment of brain tumors.

While we believe these characteristics are necessary to ensure evidence sufficient to inform providers, beneficiaries and payers of the benefits (or lack thereof) of BBBD, they are not requirements of this decision nor of the current Clinical Trial Policy.

IX. Conclusion

CMS has determined that there is sufficient evidence to conclude that the use of osmotic blood brain barrier disruption (BBBD) used as part of a treatment regimen for brain tumors in Medicare beneficiaries is not reasonable and necessary under Section 1862(a)(1)(A) of the Social Security Act.

Accordingly, we are issuing a national coverage determination (NCD) that states:

The use of osmotic blood brain barrier disruption is not reasonable and necessary when it is used as part of a treatment regimen for brain tumors. This NCD does not alter in any manner the coverage of anticancer chemotherapy.

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